Statins are independently associated with reduced mortality in patients undergoing infrainguinal bypass graft surgery for critical limb ischemia

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Objective: **Evidence suggesting a beneficial effect of cardioprotective medications in patients with lower extremity atherosclerosis derives largely from secondary prevention studies of heterogeneous populations. Patients with critical limb ischemia (CLI) have a large atherosclerotic burden with related high mortality. The effect of such therapies in this population is largely inferred and unproven.**

Methods: **The Project of Ex-Vivo vein graft Engineering via Transfection III (PREVENT III) cohort comprised 1404 patients with CLI who underwent lower extremity bypass grafting in a multicenter, randomized prospective trial testing the efficacy of edifoligide for the prevention of graft failure. Propensity scores were used to evaluate the influence of statins, β-blockers, and antiplatelet agents on outcomes while adjusting for demographics, comorbidities, medications, and surgical variables that may influence drug use. Primary outcomes were major adverse cardiovascular events ≤30 days, vein graft patency, and 1-year survival assessed by Kaplan-Meier method. Potential determinants of 1-year survival were modeled using a multivariate Cox regression.**

Results: **In this cohort, 636 patients (45%) were taking statins, 835 (59%) were taking β-blockers, and 1121 (80%) were taking antiplatelet drugs. Perioperative major adverse cardiovascular events (7.8%) and early mortality (2.7%) were not measurably affected by the use of any drug class. Statin use was associated with a significant survival advantage at 1 year of 86% vs 81% (hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.52-0.98; $P = .03$) by analysis of both unweighted and propensity score-weighted data. Use of β-blockers and antiplatelet drugs had no appreciable impact on survival. None of the drug classes were associated with graft patency measures at 1 year. Significant predictors of 1-year mortality by Cox regression modeling were statin use (HR, 0.67; 95% CI, 0.51-0.90; $P = .001$), age >75 (HR, 2.1; 95% CI, 1.60-2.82; $P = .001$), coronary artery disease (HR, 1.5; 95% CI, 1.15-2.01; $P = .001$), chronic kidney disease stages 4 (HR, 2.0; 95% CI, 1.17-3.55; $P = .001$) and 5 (HR, 3.4; 95% CI, 2.39-4.73; $P < .001$), and tissue loss (HR, 1.9; 95% CI, 1.23-2.80; $P = .003$).**

Conclusions: **Statin use is associated with improved survival in CLI patients 1 year after surgical revascularization. Further studies are indicated to determine optimal dosing in this population and to definitively address the question of relationship to graft patency. These data add to the growing literature supporting statin use in patients with advanced peripheral arterial disease. (J Vasc Surg 2008;47:774-81.)**

Peripheral arterial disease (PAD) occurs commonly, with an estimated prevalence as high as 21% in patients aged >65 years.[1-6] It has been well documented that the presence of PAD elevates the risk of cardiovascular events, including major limb loss, myocardial infarction, stroke, and death.[4,7,8] It is therefore no surprise that in the subset of patients who manifest critical limb ischemia (CLI), the most advanced form of PAD, cardiovascular event rates are high[9] and may even surpass those seen in patients with symptomatic coronary artery disease (CAD).[10]

The main emphasis on treatment for patients with CLI has tended to focus on the limb, with surgical bypass grafting and endovascular methods dominating the literature, rather than strategies of risk factor modification and stabilization of the global atherosclerotic burden.[6,11,12] Although the American Heart Association and the American College of Cardiology have endorsed a variety of prevention guideline documents for CAD patients based on level I data,[13-15] the development of treatment guidelines specific for patients with PAD has been hampered by a relative lack of robust evidence.[16]

Various reports have demonstrated that cardioprotective medications such as statins, β-blockers, and antiplatelet agents are associated with a decreased cardiovascular event rate[17-21] in the PAD population. These studies have been conducted in heterogeneous populations, however, and little is known about the effectiveness of these drugs in patient population at greatest risk—patients with CLI. In the landmark Heart Protection Study (HPS),[17] statins were clearly demonstrated to have a protective effect in

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patients with PAD, with a 22% relative reduction in major vascular events. The HPS broadly defined PAD "as a history of intermittent claudication . . . or previous peripheral arterial revascularization procedure, amputation, or aneurysm repair."[22]

Other smaller studies have examined the effects of β-blockers and statins on perioperative events in vascular surgery patients, often including aneurysm repair as a significant proportion of the cohort.[23-26] As a result, the exact role of cardioprotective medications remains unclear in patients with CLI, particularly those undergoing attempts at limb salvage. An important corollary question for CLI patients relates to the influence of these medications on the limb revascularization per se, with some recent studies suggesting improved bypass graft patency.[27-29]

This study sought to address this topic by using the Project of Ex-Vivo vein graft Engineering via Transfection (PREVENT III) database. PREVENT III was a prospective, randomized, double-blinded, multicenter trial designed to examine the efficacy of edifoligide, a novel pharmacologic agent, in preventing autogenous vein graft failure in patients who underwent an infrainguinal bypass grafting (IBG) procedure exclusively for the treatment of CLI.[30] Details of the trial design have been described elsewhere,[31] and only relevant features are briefly reviewed here. Edifoligide is a short, double-stranded DNA molecule that inhibits cell cycle gene expression and was hypothesized to reduce neointimal hyperplasia. In the primary PREVENT III analysis, however, the treatment of vein grafts with edifoligide was found to confer no benefit on the prespecified primary and secondary end points.[30] The current study used this unique database to assess the influence of cardioprotective medications on early (30-day) and mid-term (1-year) outcomes in patients undergoing vein bypass graft surgery for CLI.

PATIENTS AND METHODS

The PREVENT III cohort. The study cohort consisted of 1404 patients with CLI drawn from 83 community and university hospitals located in Canada and the United States. Each participating institution underwent independent review of the study and received approval from its respective Institutional Review Board (IRB). Enrollment was initiated in November 2001 and completed in October 2003. Pertinent characteristics of the study population are summarized in Table I, and additional detailed information may be found in the primary trial report.[30] The inclusion criteria specified patients aged ≥18 years who underwent IBG with autogenous vein for CLI, which was defined as gangrene, nonhealing ischemic ulcer, or ischemic rest pain. Exclusion criteria included claudication as an indication for IBG surgery or use of a nonautogenous conduit.

Demographic variables and a detailed vascular examination were collected before surgery as part of a comprehensive history and physical examination. The decision to prescribe any concomitant medication before, during, or after surgery was not protocol-driven and was left to the discretion of the operating surgeon. Accordingly, medication usage varied according to individual clinical practice patterns. For all patients, medication use at entry into the study (before the index surgery) and at the time of discharge (after the index surgery) was recorded by protocol.

The study subjects were followed up for 1 year from the time of IBG surgery, with graft ultrasound surveillance performed at 1, 3, 6, and 12 months, and a physical examination, including an ankle-brachial index, performed at 1, 3, 6, 9, and 12 months. Outcome events in PREVENT III were tracked by investigators and their study staff at participating centers using specifically designed case report forms, supported by source documentation. All data were audited by a contract research organization before being entered into the trial database.

Adverse event reporting ≤30 days after treatment, including major adverse cardiovascular events (MACE), was mandated by the United States Food and Drug Administration, conformed to federal regulatory guidelines (21 CFR Part 312) adverse events reporting, and used accepted clinical definitions and the Medical Dictionary for Regulatory Affairs (MedDRA, Reston, VA) preferred terminology. All MACE would be considered serious adverse events by regulatory guidelines and were therefore reported promptly to the sponsor (medical monitor) and to the local IRBs, with appropriate supporting documentation. A clinical events classification committee performed a blinded independent review of each case of index graft failure. A total of 44 patients (3.2%) either withdrew or were lost to follow-up in PREVENT III.

Study design. The cohort was analyzed to determine the influence of statin use, β-blocker use, and antiplatelet drug use on both 30-day and 1-year outcomes. Data relating to other drug categories of interest, for example, other antihypertensive classes or immunomodulatory drugs, were not available for study. For all 30-day outcome analyses, a patient's medication use category (on drug or off drug) was based entirely according to *entry* status, regardless of discharge status. Conversely, for all 1-year analyses, the patient's medication use category was based entirely according to *discharge* status, regardless of entry status.

The primary end points at 30 days were death and composite MACE, defined as any myocardial infarction, stroke, or death. The primary end points at 1 year were primary patency, secondary patency, number of rehospitalizations, and survival. All end points were defined in accordance with the published standards for outcomes reports in lower extremity revascularization[32] and assessed by the Kaplan-Meier method.

Statistical analysis. Baseline characteristics and the incidence of MACE between users and nonusers of each drug class were assessed by using the Pearson χ^2 analysis for categoric variables and the Student t test for continuous variables. Differences in primary and secondary patency and survival were compared by category for each medication class. These time-to-event end point analyses were performed by using the Kaplan-Meier method, and the treatment groups were compared with the log-rank test.

Table I. Patient characteristics in the PREVENT III cohort according to medication use recorded at time of hospital discharge

	Statin use		*β-Blocker use*		*Antiplatelet use*	
Variable	*Yes (n = 636)*	*No (n = 768)*	*Yes (n = 835)*	*No (n = 569)*	*Yes (n = 1121)*	*No (n = 283)*
Age, mean ± SD years	68.5 ± 10.5	68.5 ± 13.0	69.2 ± 11.2	67.5 ± 11.9	68.5 ± 11.6	68.9 ± 11.3
Female sex, %	38.8	33.9	36.1	36.2	35	40.6
Race/ethnicity, %						
Caucasian	76.4[a]	69.1[a]	73.7	70.7	74.2[a]	65.4[a]
African American	13.4[a]	21.4[a]	16.7	19.3	16.4[a]	23.0[a]
Other	10.2	9.5	9.7	10	9.37	11.7
Risk factors for PAD, %						
Smoking	73.9	73.7	71.4[a]	77.3[a]	74.6	70.7
High cholesterol	73.3[a]	21.9[a]	50.5[a]	37.3[a]	45.9	42.4
Diabetes mellitus	72.0[a]	57.6[a]	67.5[a]	59.1[a]	65.6[a]	58.3[a]
Hypertension	85.4[a]	78.5[a]	87.7[a]	72.8[a]	81.8	80.9
CAD	52.7[a]	32.7[a]	48.9[a]	31.3[a]	44.5[a]	30.7[a]
Dialysis-dependent	12.6[a]	17.7[a]	14.4[a]	16.9[a]	14.5[a]	19.1[a]
Prior IBG	32.6[a]	22.9[a]	28.7	25.1	26.7	29.7
CLI criterion, %[b]						
Rest rain	24.5	22.3	24.1	27.6	26.2	22.6
Tissue loss	75.5	73.7	75.9	72.4	73.8	77.4
Medications, %						
Statin	100[a]	0[a]	51.1[a]	36.7[a]	47.5[a]	52.5[a]
β-blocker	67.1[a]	53.1[a]	100[a]	0[a]	62.1[a]	49.1[a]
Aspirin	83.8[a]	76.6[a]	83.4[a]	74.7[a]	100[a]	0[a]
Edifoligide	49.7	50.9	50.8	49.7	48.8	53
Surgical characteristics, %						
Proximal anastomosis						
CFA	46.7	50.8	48.3	49.9	48.9	49.1
SFA	25.3	24.2	24.1	25.7	24.5	25.4
Popliteal	16.7	17.5	18	15.8	17.1	17
Distal anastomosis						
Popliteal	33	32.2	30.9	35	32	34.6
Tibial	52.5	53.9	53.9	52.4	53.4	53
Pedal	11.3	12.2	12.8	10.4	12	11
Conduit diameter						
<3 mm	5.5	6.51	4.55	8.26	6.24	5.3
3-3.49 mm	37.1	40.1	38.3	39.4	38.6	39.2
>3.5 mm	52.2	50.8	51.7	51	50.8	54.1
Institutional setting, %						
US, academic	62.9[a]	54.3[a]	68.1[a]	43.6[a]	62.0[a]	43.1[a]
US, private	29.7[a]	39.8[a]	25.8[a]	49.2[a]	31.3[a]	50.9[a]
Canada	7.39	5.86	6.11	7.2	6.7	6.01

CAD, Coronary artery disease; *CFA,* common femoral artery; *CLI,* critical limb ischemia; *IBG,* infrainguinal bypass graft; *PAD,* peripheral arterial disease; *PREVENT III,* Project of Ex-Vivo vein graft Engineering via Transfection; *SFA,* superficial femoral artery; *US,* United States.

[a] $P < .05$. Propensity scoring was used to generate weights in order to balance all covariates above resulting in no significant differences between groups (see Appendix Table, online only).

As described initially by Rosenbaum and Rubin,[33] the generation of a propensity score to predict the probability of exposure to a certain treatment enables one to control for the aggregate amount of measured confounding. Accordingly, to adjust for different baseline demographic, comorbid, and surgical covariates (Table I), propensity score models were created for each drug class. In this propensity score approach, the data for each patient were weighted by the product of the inverse of the probability of receiving his or her treatment given the demographic and surgical characteristics specified in Table I with the baseline probability of group membership. Once these weights were obtained and assessed for functionality of achieving balance in previously unbalanced covariates (Appendix Table, online only), they were applied to subjects in a univariate proportional hazards model comparing the treatment strategies.

Finally, a separate Cox proportional hazards model with backwards elimination was used to identify independent predictors for 1-year mortality. Variables incorporated in this model were:

- demographics—age, sex, race, institutional setting;
- PAD risk factors—tobacco use, diabetes mellitus, hypertension, CAD, prior coronary artery bypass graft, chronic kidney disease class, prior IBG;
- CLI criterion—rest pain, tissue loss;
- medication usage—statin, β-blocker, antiplatelet; and

Table II. Early (30-day) major adverse cardiovascular events and death according to statin, β-blocker, and antiplatelet use,[a] before and after propensity model weighting

	Statin use			*β-Blocker use*			*Antiplatelet use*		
Variable	*Yes*	*No*	P	*Yes*	*No*	P	*Yes*	*No*	P
MACE, %									
Unweighted	8.7	7	.23	9.5	6.2	.02	8.7	5.8	.06
Weighted	7.4	7.1	.84	9	7.4	.28	8.9	6.6	.2
Death, %									
Unweighted	2.6	2.7	.92	2.7	2.6	.94	3.2	1.5	.06
Weighted	2.2	2.7	.5	2.6	3	.67	3.4	1.6	.06

MACE, Major adverse cardiovascular event.
[a]Medication use recorded at time of hospital admission.

Table III. Patency and survival at 1 year according to statin, β-blocker, and antiplatelet use,[a] before and after propensity model weighting

	Statin use			*β-Blocker use*			*Antiplatelet use*		
	Yes	*No*	P	*Yes*	*No*	P	*Yes*	*No*	P
Primary patency, %									
Unweighted	55.1	55.6	.78	57.7	52	.02	54.9	56.7	.65
Weighted	56.2	55.5	.8	57.7	53.8	.16	55.2	60.6	.12
Secondary patency, %									
Unweighted	76	76.8	.61	77.7	74.3	.08	77.5	73.3	.23
Weighted	76	76.8	.66	77.5	75.1	.19	77.6	76.2	.73
Survival, %									
Unweighted	85.9	81.2	.02	82.8	84.1	.49	83.9	81	.26
Weighted	86	81.4	.04	83.2	83.7	.66	83.9	81.5	.38

[a]Medication use recorded at time of hospital discharge.

- surgical characteristics—anastomoses site, conduit diameter.

Comparisons of the number of rehospitalizations were made with Wilcoxon rank sum tests for nonparametric data. All tests were considered statistically significant at $\alpha = .05$ ($P = .05$, two-tailed). All analyses were performed using SAS 9.1 software (SAS Inc, Cary, NC).

RESULTS

Early (30-day) major adverse cardiovascular events and death. For the 1404 patients in the entire study cohort, the incidence of MACE was 7.8% and the 30-day mortality rate was 2.6%. Use of any of the studied drug classes was not found to be significantly associated with either MACE or death at 30 days (Table II). Although use of β-blockers was associated with the incidence of 30-day MACE (9.5% vs 6.2%, $P = .02$) in the unadjusted data, this effect lost significance once propensity score weighting was used (9.0% vs 7.4%, $P = .28$). It should be noted that although the data reported for 30-day outcomes used medications recorded at study entry (see "Methods"), these analyses were repeated using discharge medication data, with no significant difference in the findings.

Graft patency at 1 year. No association was found between any drug class and 1-year primary or secondary graft patency (Table III). In the unadjusted analysis, a statistically significant 1-year primary patency advantage was seen in the patients taking β-blockers. However, this effect was not significant when the data were adjusted by the propensity score model (57.7% vs 53.8%, $P = .16$).

Cumulative number of patient rehospitalizations occurring more than 1-year after bypass graft surgery. The mean number of rehospitalizations during the year after bypass graft surgery was 1.53 for the entire study population. Patients taking β-blockers required significantly more rehospitalizations (1.61 vs. 1.41, $P = .03$) during the year after surgery (Table IV). Neither statin use nor antiplatelet agent use was associated with the number of required rehospitalizations.

When the cause for admission was limited to cardiovascular etiology specifically, the mean number of required rehospitalizations for the entire cohort decreased to 0.16. None of the cardioprotective medications, other than β-blockers (0.18 vs 0.12, $P = .02$), demonstrated a significant association with the number of required cardiovascular rehospitalizations.

Survival at 1 year. The overall Kaplan-Meier estimate for 1-year survival in the PREVENT III cohort was 84%. A significant survival advantage was seen in patients taking statins compared with those not prescribed statins (Fig). This effect was seen on the unadjusted analysis (85.9% vs 81.2%, $P = .02$) and persisted on the propensity score–

Table IV. Cumulative number of rehospitalizations at 1 year according to statin, β-blocker, and antiplatelet use recorded at time of hospital discharge

	Statin use			*β-Blocker use*			*Antiplatelet use*		
Rehospitalizations	*Yes*	*No*	P	*Yes*	*No*	P	*Yes*	*No*	P
Total No.	1.6	1.5	.37	1.6	1.4	.03	1.5	1.5	.89
Cardiovascular, No.	0.16	0.15	.73	0.18	0.12	.02	0.16	0.13	.34

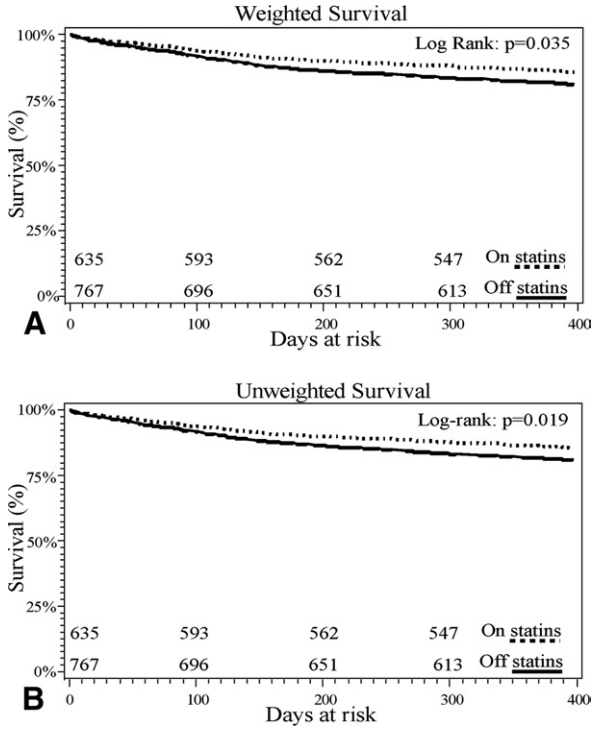

Fig. One-year survival by the Kaplan-Meier method according to patients who were taking statins *(dashed line)* vs not taking statins *(solid line)* recorded at the time of hospital discharge. **A,** Weighted propensity score for survival ($P = .03$). **B,** Unweighted propensity score for survival ($P = .02$).

adjusted analysis (86.0 vs 81.4%, $P = .04$). At 1 year, patients taking statins had a hazard ratio (HR) of death of 0.71 (95% confidence interval [CI] 0.52-0.98; $P = .03$). Neither β-blocker use nor antiplatelet drug use was associated with 1-year survival (Table III).

A multivariable Cox regression model of survival (Table V) that controlled for demographic variables, PAD risk factors, CLI criterion, medication usage, and surgical characteristics also identified statin use as a significant predictor of 1-year mortality (HR, 0.68; 95% CI, 0.51-0.90; $P < .01$). Additional significant independent predictors of mortality were age >75 (HR, 2.13; 95% CI, 1.60-2.82), presence of CAD (HR, 1.52; 95% CI, 1.15-2.01), chronic kidney disease stages 4 (HR, 2.04; 95% CI, 1.17-3.55) and 5 (HR, 3.4; 95% CI, 2.39-4.73), and tissue loss (ulcer or gangrene) on presentation (HR, 1.86; 95% CI, 1.23-2.80).

Table V. Multivariate analysis identifying impact of predictors of mortality at 1 year in the PREVENT III population

Variable	*Hazard ratio (95% CI)*	P
Age >75	2.13 (1.60-2.82)	<.01
Female sex	1.09 (0.81-1.46)	.58
Race/ethnicity		
White	1.0 (ref)	. . .
African American	0.82 (0.56-1.20)	.3
Other	0.97 (0.63-1.50)	.9
Risk factors for PAD		
Smoking	0.93 (0.68-1.28)	.65
Diabetes mellitus	1.31 (0.96-1.79)	.09
Hypertension	1.04 (0.70-1.54)	.84
Coronary artery disease	1.52 (1.15-2.01)	<.01
Prior IBG	0.84 (0.61-1.16)	.3
Chronic kidney disease		
Stage 4	2.04 (1.17-3.55)	.01
Stage 5	3.36 (2.39-4.73)	<.01
CLI criterion[a]		
Rest pain	1.0 (ref)	. . .
Tissue loss	1.86 (1.23-2.80)	<.01
Medications		
Statin	0.68 (0.51-0.90)	<.01
β-blocker	1.10 (0.82-1.46)	.52
Aspirin	0.86 (0.63-1.19)	.37
Surgical characteristics		
Proximal anastomosis		
CFA	1.0 (ref)	. . .
SFA	0.89 (0.64-1.23)	.47
Popliteal	0.65 (0.42-1.00)	.05
Distal anastomosis		
Popliteal, AK	1.0 (ref)	. . .
Popliteal, BK	1.22 (0.86-1.72)	.26
Tibial	0.82 (0.48-1.40)	.48
Pedal	0.86 (0.54-1.36)	.52
Conduit diameter		
<3 mm	1.40 (0.85-2.30)	.19
3-3.49 mm	0.83 (0.62-1.10)	.21
>3.5 mm	1.0 (ref)	. . .
Institutional setting		
US, academic	0.90 (0.68-1.20)	.48
US, private	1.0 (ref)	. . .
Canada	0.54 (0.27-1.09)	.09

AK, Above knee; *BK,* below the knee; *CFA,* common femoral artery; *CLI,* critical limb ischemia; *IBG,* infrainguinal bypass graft; *PAD,* peripheral arterial disease; *PREVENT III,* Project of Ex-Vivo vein graft Engineering via Transfection; *SFA,* superficial femoral artery; *US,* United States.
[a]Most severe.

DISCUSSION

Patients who present with CLI bear a large systemic burden of atherosclerotic disease and therefore face not only the immediate risk of limb loss[34] but also an increased

risk for cardiovascular events.[7-9] Although this population would seemingly have much to gain from the use of cardioprotective medications, the efficacy of these drugs in the setting of such globally advanced atherosclerosis cannot be assumed from other cohorts. The PREVENT III trial, with its high-risk CLI population, provides a relevant database for examination. The salient finding of this study is that the use of statin drugs was associated with a significant 1-year survival benefit in patients undergoing surgical bypass grafting for CLI. The Kaplan-Meier analysis further suggests that the benefit continues to increase with time and might be even greater with longer-term follow-up.

A previously published report by the PREVENT trialists examined the determinants of usage of medications and their effects on immediate perioperative outcomes.[35] The present study adds to this work by using sophisticated models to assess the effect of cardioprotective medications on both 30-day and 1-year outcomes. The patients in this cohort of 1404 who did not receive statins experienced an approximate 40% increase in the risk of death at 1-year. This effect was demonstrated both in the propensity score–weighted analysis (HR, 1.40; 95% CI, 1.02-1.92) and in the Cox proportional hazards model (HR, 1.47; 95% CI, 1.11-1.96).

These findings are consistent with observational studies that have examined the effects of statins, albeit in heterogeneous PAD populations.[18,23,36] The largest of these, conducted by Feringa et al,[18] enrolled 1374 patients with PAD and monitored them for a mean duration of 6.4 years. The authors demonstrated a strong independent association between statin use and all-cause mortality (HR, 1.41 for nonusers; $P < .0001$).[18]

The HPS is the largest trial to assess the effects of statins on major morbidity and mortality.[17] The investigators enrolled >20,000 patients deemed to be at high risk for cardiovascular events and randomized them to receive either simvastatin (40 mg) or placebo. The survival analysis demonstrated that treatment with a statin was significantly associated with a decrease in all-cause mortality (12.9% vs 14.7%, $P = .0003$) and that this effect was primarily driven by the reduction in death from vascular causes (7.6% vs 9.1%, $P < .0001$). A recently published subgroup analysis[22] focusing specifically on 6748 patients with documented PAD did not include mortality data or stratify the patients according to the degree of limb ischemia. However, the authors demonstrated a significant relative reduction of 22% in the rate of a first major vascular event in the simvastatin treatment arm ($P < .0001$) compared with placebo.

A wide body of literature has developed showing that β-blockers[24,37,38] and antiplatelet agents[20,39] provide benefit in patients with PAD, including those undergoing vascular reconstructions. Statin therapy has also been recently associated with decreased perioperative morbidity and mortality[25,26,36] in vascular surgery patients. Thus, the negative findings for both perioperative and long-term events in this study must be interpreted with great caution and have several important limitations.

First and foremost, patients were not randomized to treatment with these medications in PREVENT III. At the time PREVENT III was initiated, extensive data were already available suggesting a benefit for β-blockers and antiplatelet agents in peripheral vascular patients, although much less so for statins (note the HPS study was published 1 year after PREVENT III began enrollment). This was reflected by the relative use of these drug classes in the cohort, suggesting important differences in prescribing patterns. It is possible that the appropriate patients—those in most need of aggressive medical management—were selected for β-blocker and antiplatelet agent treatment upfront by their physicians (confounding by indication). As a result, if the treated patients were at higher baseline risk than those not treated, a significant drug effect would be difficult to identify.

Propensity score modeling has been used in this situation to effectively control for the aggregate amount of confounding contributed by various factors.[33,40,41] Nonetheless, although this methodology tries to emulate the advantages of a randomized trial, it does not achieve them completely; unlike a randomized trial that controls for measured and *unmeasured* confounders, a propensity score can only equalize observed confounders between groups. Therefore, the failure to see an association between β-blockers or antiplatelet agents with the outcomes measured in this study may be due to the presence of unrecognized confounders that were not included in the propensity score models.

Second, this study may have lacked statistical power to demonstrate certain associations. This is particularly relevant to the analysis of 30-day outcomes where the limited number of events has been noted in this and other studies.[42] Analysis of some 1-year outcomes may also have been limited by power. Looking at β-blockers as an example, although the power to detect a 20% graft patency difference was >80% ($\alpha = .05$, HR, 1.20; total number events, 554), the power to detect a 20% survival difference was well below 80% ($\alpha = .05$; HR, 1.20; total number events, 228). For antiplatelet therapy, the combination of a small cohort of nonusers (20%) and a limited number of events greatly reduces the ability to measure benefit in this study.

Because of the aforementioned limitations inherent to the context of this study, failure to show an association between certain outcomes and medications on this analysis should be considered hypothesis generating only. Specifically, we would not advocate any change in the use of β-blockers and antiplatelet agents in this high-risk population, and we continue to prescribe them for our patients. However, this study highlights that the optimal approach to reduce short- and long-term cardiovascular risk remains undefined for the CLI patient and requires further prospective investigation.

Some recent reports have suggested a potential benefit for graft patency for patients using statin drugs.[27,29,43] In this analysis, we did not observe any significant relationship between statin use and graft outcomes. The study by Abbruzzese et al[27] contrasts with the PREVENT III cohort in

several important ways, including single-center experience, a lower-risk nature of the conduits used (all single-segment great saphenous veins), no reoperative cases, and a longer duration of follow-up.[27] In contrast, the PREVENT III population included a significant proportion of high-risk conduits (23% were nonsingle segment great saphenous vein grafts), including 17% reoperative cases, that were performed in 83 hospitals in the trial.

Of note, recent work has suggested that systemic inflammation, as measured by levels of high-sensitivity C-reactive protein, may be linked to cardiovascular events and vein graft failure in patients undergoing lower extremity bypass graft surgery.[44] The anti-inflammatory properties of statins may therefore provide a plausible mechanism for benefit in patients undergoing bypass graft surgery, adding to the rationale for prospective studies to definitively address this question.

Finally, this data set contains only two static time points detailing whether or not a patient was receiving statin therapy. No data were available on dosages, the duration of treatment either before or after surgery, or on the degree of patient compliance with prescribed medications.

One salient feature of this analysis that deserves reemphasis is the underutilization of the three drug categories studied. In this cohort, at the time of discharge after major reconstructive vascular surgery, only 45% of patients were prescribed statins, 59% were prescribed β-blockers, and 80% were prescribed antiplatelet agents. This undertreatment of patients with PAD has been echoed by several other published reports[6,11,12] and deserves more attention.

CONCLUSIONS

To our knowledge, this is the first report to demonstrate that statin use is associated with improved survival, specifically in CLI patients, 1-year after surgical revascularization. Further studies are indicated to determine optimal dosing in this high-risk population and to definitively address the question of effects on graft patency. These data add to the growing literature supporting statin use in patients with advanced PAD.

AUTHOR CONTRIBUTIONS

Conception and design: AS, MSC
Analysis and interpretation: AS, NH, MSC
Data collection: MSC
Writing the article: AS, MSC
Critical revision of the article: AS, NH, CO, JB, MSC
Final approval of the article: AS, NH, CO, JB, MB, MSC
Statistical analysis: AS, NH
Obtained funding: AS, MSC
Overall responsibility: MSC

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Appendix Table (online only). Patient characteristics in the PREVENT III cohort according to medication use after weighting by the propensity score[a]

	Statin use[a]		β-*Blocker use*[a]		*Antiplatelet use*[a]	
Characteristic	*Yes*	*No*	*Yes*	*No*	*Yes*	*No*
Age, mean ± SD years	68.6 ± 12.1	68.6 ± 11.4	68.7 ± 11.6	68.5 ± 11.1	68.5 ± 11.6	68.9 ± 11.3
Female sex, %	35	36.1	35.9	36.1	36.1	35.7
Race/ethnicity, %						
Caucasian	73.8	72.3	72.3	71.7	72.5	71.9
African American	16.9	17.9	17.4	17.8	17.1	17.1
Other	9.3	9.8	10.3	10.5	10.4	11
PAD risk factors, %						
Smoking	73.7	73.8	73.7	75.5	73.6	72.7
High cholesterol	. . .	. . .	44.9	43.6	45.2	45.4
Diabetes mellitus	62.5	63.5	64.4	65.1	64.1	64.7
Hypertension	79.3	81.7	82.4	82	81.7	83.3
CAD	40.2	41.4	42.3	41.9	41.8	42.1
Dialysis-dependent	13.3	15.4	16.1	15.6	15.4	16.4
Prior IBG	26.8	27	26.5	25.7	27.2	26.5
CLI criterion, %						
Rest pain	24.6	25.6	25.6	24.6	25.4	26.2
Tissue loss	75.4	74.4	74.4	75.4	74.6	73.8
Medications, %						
Statin	. . .	. . .	46.7	46	49.8	49.9
β-Blocker	57.6	59.1	. . .	. . .	59.6	60.4
Aspirin	80.7	79.8	80.5	80	. . .	. . .
Edifoligide	47.9	48.4	49.8	48.4	49.8	51.6
Surgical characteristics, %						
Proximal anastomosis						
CFA	48.4	49.8	48.7	50.8	49	49.9
SFA	27.4	25	24.9	22.7	24.7	24.9
Popliteal	15.7	16.9	17.2	17.3	17.2	17.6
Distal anastomosis						
Popliteal	30.5	32.8	32.6	31.8	32.9	32.4
Tibial	56	53.4	53.3	55.8	53.5	53.4
Pedal	11.1	11.8	11.5	10.3	11.7	11.2
Conduit diameter						
<3 mm	5.76	6.12	5.86	5.43	5.99	6.36
3-3.49 mm	37.9	38.6	37.6	38.4	38.7	37.2
>3.5 mm	52.7	50.9	52.9	52.1	51.5	52.2
Institutional setting, %						
US, academic	58.9	58.2	58.5	58.1	58.2	57.8
US, private	35.7	35.2	35	35.4	35.2	36.3
Canada	5.85	6.09	6.54	6.54	6.52	5.93

CAD, Coronary artery disease; *CFA,* common femoral artery; *CLI,* critical limb ischemia; *IBG,* infrainguinal bypass graft; *PAD,* peripheral arterial disease; *PREVENT III,* Project of Ex-Vivo vein graft Engineering via Transfection; *SFA,* superficial femoral artery; *US,* United States.

[a]All values of $P > .05$.